

## REMARKS

### Introductory Comments

Applicants acknowledge that claims 1, 2, 4-6, 10, 11 and 20-25 are presented for examination.

### The Rejections

#### 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 2, 4-6, 10, 11 and 22 under 35 U.S.C. § 103(a) as being unpatentable over Montgomery (US 4,210,745) (hereinafter “Montgomery”) in view of Stamos et al. (WO 00/56331) (hereinafter “Stamos”). According to the Examiner, Montgomery teaches fludarabine, a compound known to possess anticancer properties. The Examiner further contends that Stamos teaches compounds of the same structural formula (A) useful to treat cancers and tumors. The Examiner concludes that “one skilled in the art would have assumed the combination of two individual agents well-known as anticancer agents into a single composition would give an additive effect in the absence of evidence to the contrary.” Applicants respectfully traverse for the following reasons.

First, Montgomery and Stamos do not teach or suggest the claimed combination of the present invention; namely the use of an IMPDH inhibitor of formula A in combination with an apoptosis inducing, anti-cancer and anti-metabolite agent such as fludarabine. Montgomery teaches a procedure for preparing the anti-cancer agent fludarabine. Stamos teaches a genus of IMPDH inhibitors of formula A useful to treat cancers and tumors either alone or in combination with an additional anti-cancer agent. However, the specific combination of fludarabine with a compound of formula A is neither taught nor suggested by Montgomery or Stamos. Therefore, one skilled in the art would not have been motivated nor would have found it obvious to make the combination of the present invention based on the species disclosed in Montgomery and the genus and combination disclosed in Stamos.

Second, the claimed combination of the present invention, namely an apoptosis inducing, anti-cancer agent (e.g., fludarabine) with an IMPDH inhibitor of formula A, imparts a surprising and unexpected synergistic rather than additive (emphasis added) increase in anti-cancer activity. Specifically, the claimed combination synergistically increases a cancer cells susceptibility to

apoptosis and cell death. For instance, applicants have provided data (see, specification, Example 1, paragraphs [0065] to [0069] at pages 58-59) for the combination of representative compound number 181 either alone or in combination with fludarabine to evaluate the apoptotic effect (measured by percent apoptosis) on a Daudi cancer cell line. Figures 1 and 2 provide a graphical readout of the observed synergistic effects. Figure 1 shows the percent apoptosis against the concentration of compound 181 alone, fludarabine alone, and a combination of both agents. Therein, the combination of compound 181 and fludarabine results in a much greater percent apoptosis due to the synergy therebetween. Moreover, Figure 2 provides a graphical representation of the strong synergistic effect observed with the fludarabine/compound 181 combination. Therein, a CalcuSyn analysis of percent apoptosis (using the Guava Nexin assay to detect Annexin-Positive Daudi cells; see specification, Example 1, paragraph [0065]) shows a strongly synergistic effect at all three doses tested namely, the ED50, ED75 and the ED90. Thus, the unexpected synergistic effect (as opposed to merely additive) observed for the claimed combination of the present invention renders it a non-obvious, patentable invention over Montgomery in view of Stamos.

In summary, the claimed combination of the present invention that provides a genus of compounds of formula A and an apoptosis inducing anti-cancer agent such as fludarabine is neither taught nor suggested by Montgomery or Stamos. Furthermore, the unexpected synergistic effect and enhanced anti-cancer profile possessed by the claimed combination renders it non-obvious over Montgomery in view of Stamos. Accordingly, applicants respectfully request that the Examiner this § 103(a) rejection.

#### Non-statutory Double Patenting

The Examiner has rejected claims 1, 2, 4-6, 10, 11 and 22 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-11 of U.S. Patent No. 6,498,178 (hereinafter the “‘178 patent”). Applicants respectfully traverse.

As discussed above, the claimed combination of the present invention provides an unexpected synergistic effect resulting in an enhanced anti-cancer profile. The ‘178 patent provides no teaching, suggestion or motivation to select the claimed combinations. Therefore, the present application is an unobvious, patentable invention over the ‘178 patent. Accordingly,

applicants respectfully request that the Examiner withdraw this nonstatutory double patenting rejection.

Conclusion

Applicants respectfully request that the Examiner consider the foregoing remarks and allow the pending claims to pass to issue.

Respectfully submitted,

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